

Prevention of VZV Infection in Immunosuppressed Patients Using Antiviral Agents

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KEY WORDS

■ VARICELLA ZOSTER VIRUS ■ ACICLOVIR ■ REACTIVATION ■ POST-EXPOSURE PROPHYLAXIS ■ IMMUNOSUPPRESSED PATIENTS

SUMMARY

Antiviral agents play a key role in the prevention and treatment of varicella zoster virus (VZV) disease in immunosuppressed patients. Randomized trials show that aciclovir is effective in preventing VZV reactivation disease; however, no consensus exists on dose, duration and patient population for its use. The recent shortage of VZV-specific immunoglobulin has generated renewed interest in the use of antiviral agents as post-exposure prophylaxis. The use of antiviral agents for post-exposure prophylaxis is not supported by randomized trials, but uncontrolled experience suggests that it might be a reasonable alternative if varicella-specific immunoglobulin is not available. Current evidence on the use of antiviral agents in the prevention of reactivation disease and management of exposure to VZV is discussed.

Introduction

VARICELLA ZOSTER VIRUS (VZV) remains an important pathogen in immunosuppressed patients. In immunocompetent individuals, vaccination strategies are used towards disease eradication. However, no vaccine strategies have been developed for immunosuppressed patients. In this patient population, both primary and reactivation disease present major clinical risks. While reactivation disease can be prevented by antiviral agents, no consensus exists on dose and duration of preventative strategies. For primary infection, the use of VZV-specific immunoglobulin (VZIG) is recommended within 96 h following exposure. However, only moderate efficacy and a recent shortage of VZIG has raised the question whether antiviral agents can be used instead of, or even in combination with, VZIG. This article reviews current data on the use of antiviral agents for reactivation disease and following exogenous exposure.

Clinical Significance, Risk Factors and Disease Management

Varicella zoster virus can cause serious morbidity and mortality in immunosuppressed patients, especially after haematopoietic cell transplantation (HCT).¹ VZV reactivation occurs in 30–60% of VZV-seropositive recipients with most cases occurring after 3 months after transplantation (Figure 1).^{2–6} Risk factors have been defined in numerous studies and include allogeneic transplants, use of total body irradiation, *in vivo* or *ex vivo* T-cell depletion and recipient age (>10 years). Autologous transplant recipients are also at risk for developing VZV disease, although the incidence is somewhat lower than that following allogeneic

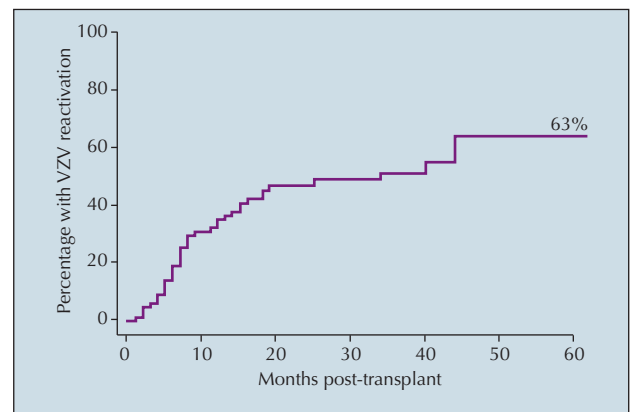


Figure 1: Estimated incidence of varicella zoster virus (VZV) reactivation in 100 consecutive allogeneic haematopoietic cell transplant recipients without long-term prophylaxis. The patients who remained VZV infection-free were recorded at the time of their last follow-up or death. Adapted from Koc Y et al. *Varicella zoster virus infections following allogeneic bone marrow transplantation: frequency, risk factors, and clinical outcome.* *Biol Blood Marrow Transplant* 2000;6:44–49. Reproduced with permission from the American Society for Blood and Marrow Transplantation.³

transplantation.^{2–4} Graft-versus-host disease has not been consistently associated with a higher risk of VZV disease.^{2,4,6,7} The risk after umbilical cord blood transplantation seems to be at least as high as that after bone marrow transplantation.⁷ Limited data exist on disease risk after peripheral blood stem cell transplantation and following transplantation with non-myeloablative or reduced toxicity conditioning regimens; however, initial data suggest that the risk of VZV infection may be similar to that observed after myeloablative marrow transplantation.^{8,9} VZV reactivation is also observed after solid organ transplantation,^{10,11} in the setting of chemotherapy¹² and following administration of anti-T-cell antibodies, such as alemtuzumab.¹³

Clinically, approximately 80% of reactivation disease presents as localized herpes zoster; 20% presents as disseminated disease. Syndromes of importance include trigeminal zoster with keratitis, retinal necrosis, encephalitis, myelitis, Ramsay-Hunt syndrome, post-herpetic neuralgia and local scarring or bacterial superinfection; these complications occur in up to one third of patients with VZV infection.^{2,14–17} Hospitalization is often required with disseminated disease.^{2,18–20} VZV disease can occasionally be fatal, even if treated with aciclovir; most fatalities occur during the first year after allogeneic HCT.^{2–4} Furthermore, hepatic or gastrointestinal VZV disease

may occur with few or no skin lesions, which often delays the diagnosis, leading to a high fatality rate.^{2,21–34}

Varicella zoster virus-seronegative HCT recipients are at risk of primary VZV infection from either wild-type or vaccine strains. VZV disease in seronegative recipients is rarer than in seropositive HCT recipients, but may still occur in up to 20% of patients.⁴ The risk of reactivation of vaccine strains in the HCT population has not been evaluated. An earlier study, in vaccinated children with acute leukaemia undergoing chemotherapy, demonstrated a low rate of zoster.¹² Since the varicella vaccine is only 87% effective,³⁵ some transplant candidates may harbour both the vaccine and the wild-type strain.

Primary VZV disease in an immunocompromised individual can be very severe; thus, strict infection control measures are taken to prevent exposure, and early intervention is recommended post-exposure.³⁶

Treatment of disseminated VZV disease is with high-dose aciclovir (given intravenously, adults: 500 mg/m² or 10–12 mg/kg three times daily; children under 12 years of age: 20 mg/kg, every 8 h). After no more lesions are detected and all existing lesions are crusted, treatment may be completed with oral valaciclovir at 1000 mg three times daily. Localized zoster not involving the trigeminal nerve may be treated with oral valaciclovir (1000 mg three times daily) or famciclovir (500 mg three times daily), provided that the patient has good oral intake. There is no evidence that intravenous immunoglobulin, VZIG or corticosteroids add significant benefit in the treatment of clinical disease in immunocompromised patients.

Prevention Strategies for VZV Reactivation Disease Using Antivirals

Several antiviral drugs have anti-VZV activity, including aciclovir, famciclovir, valaciclovir, ganciclovir, foscarnet, cidofovir, vidarabine and brivudin.³⁷ Aciclovir and its derivatives are the most commonly used drugs due to their high efficacy and excellent safety profiles. Although ganciclovir and foscarnet are not used for first-line prophylaxis, these drugs are effective and provide sufficient protection when given for cytomegalovirus prevention.³⁸ Aciclovir has been studied extensively for the prevention of VZV reactivation disease after HCT; these studies indicated that the drug is highly effective during

the time when it is given, even at low doses (Table 1). Breakthrough disease is extremely rare in patients who take the drug, and drug resistance has not been described in this setting to date. Indeed, patients who do have breakthrough disease generally respond to high-dose intravenous aciclovir.^{43,45}

Despite its efficacy in preventing VZV disease, aciclovir prophylaxis was not recommended as routine prophylaxis in the guidelines published in 2000 by the Centers for Disease Control and Prevention, the American Society of Blood and Marrow Transplantation and the Infectious Diseases Society of America.³⁶ The reluctance to recommend prophylaxis was based on observations in earlier studies which showed that VZV disease continued to occur after drug discontinuation, so that there was no difference in disease incidence rates at later time-points (Table 1). One study that used aciclovir prophylaxis for 6 months also described a suppression of VZV-specific T-cell responses in aciclovir recipients.³⁴ Thus it was postulated that aciclovir prophylaxis delayed VZV-specific immune reconstitution, thereby leading to a disproportionately strong increase of VZV disease after drug discontinuation ('rebound disease').³⁴ A recently published study found somewhat different results, however.⁴⁵ A higher dose of aciclovir (800 mg twice daily), given for 1 year post-transplant, had no effect on T-cell immunity at 1 year. VZV disease did occur after drug discontinuation, but it was seen predominantly in patients with ongoing immunosuppression, and the use of aciclovir during the first year was not statistically significantly associated with late VZV disease.⁴⁵ In a subsequent, large, population-based study, there was also no detectable 'rebound effect' in aciclovir recipients.⁴⁶ These data suggest that late VZV disease is due to continued immunosuppression in a significant number of patients and that aciclovir use *per se* may not be responsible for late occurrences.

There are no controlled data on whether aciclovir derivatives, such as valaciclovir or famciclovir, offer additional benefit compared with aciclovir in the prevention of VZV reactivation in HCT recipients or other immunosuppressed patients. Studies suggest that aciclovir is basically 100% effective (Table 1), even in the presence of severe graft-versus-host disease and associated immunosuppression.^{39,43–45} However, valaciclovir may allow for once-a-day drug administration or show more complete suppression of

Table 1: Aciclovir drug regimens used to prevent varicella zoster virus (VZV) reactivation disease in haematopoietic cell transplant recipients

| Adult dose | Study design | n | Breakthrough VZV disease during prophylaxis (%) | VZV disease after discontinuation of prophylaxis | Reference |
|---------------------------|---------------|-----|---|--|-----------|
| 400 mg, three times daily | Randomized | 21 | 0 | Yes | 34 |
| 800 mg, four times daily | Randomized | 42 | 0 | Yes | 39 |
| 400 mg, three times daily | Observational | 21 | 0 | Yes | 40 |
| 800 mg, four times daily | Randomized | 210 | 3 | Yes | 41 |
| 400 mg, three times daily | Observational | 28 | 0 | Yes | 42 |
| 400 mg, once daily | Observational | 45 | 0 | Yes | 43 |
| 200 mg, twice daily | Observational | 247 | 0.4 | Yes | 44 |
| 800 mg, twice daily | Randomized | 38 | 5 (0) ^a | Yes | 45 |

^aResults of the intent-to-treat analysis and an on-treatment analysis in parentheses.

herpes simplex virus (HSV) infection and disease, including drug-resistant HSV disease.⁴⁶

Prevention of VZV Acquisition During Immunosuppression

TRANSPLANTATION CANDIDATES AND THEIR CAREGIVERS

Candidates for transplantation (and their caregivers and potential visitors with no history of chickenpox or known negative VZV serology) should be instructed to be vaccinated using the licensed live-attenuated vaccine prior to the transplantation.³⁶ Whether vaccinating seronegative donors or those with a negative history is beneficial for the recipient is unknown, but the risk is negligible and there is the theoretical benefit of adoptive transfer of donor immunity. These issues should be raised during the initial contact with the transplant centre. Since vaccine rashes and shedding may occur occasionally, the vaccination regimen should commence approximately 3–4 weeks prior to the transplantation.³⁶ If a seronegative unvaccinated family member or caregiver is exposed, contact should be avoided during the expected period of clinical disease (Day 8–21 after exposure). Post-exposure vaccination of the family member or caregiver should be considered.⁴⁷ If contact cannot be avoided during the expected time-period of the rash, post-exposure antiviral prophylaxis may be considered.⁴⁷ If a rash occurs despite this, the post-exposure measures of the HCT recipients should be employed (see the section on the management of VZV exposure).

TRANSPLANT RECIPIENTS

Seronegative transplant recipients who could not be vaccinated before transplantation should be carefully watched for possible exposures and clinical disease after transplantation. Because the effectiveness of chemoprophylaxis (e.g. with aciclovir) in these patients has not been studied, it is not recommended in these patients.³⁶

Management of VZV Exposure

SERONEGATIVE RECIPIENTS

Within 96 h of an exposure to VZV, it is recommended that VZIG is administered to a seronegative recipient.³⁶ However, even with VZIG, the disease is not completely prevented and a mild rash may still occur.⁴⁸ Thus, the

additional use of antiviral drugs has been suggested.⁴⁹ The shortage of VZIG that occurred in 2006 has also raised the question whether antiviral drugs can be used post-exposure instead of VZIG. The strategy has not been evaluated in randomized clinical trials. However, data from immunocompetent VZV-exposed children suggest that antiviral drugs can mitigate the disease (Table 2).^{50,51} Interestingly, the available data from immunocompetent subjects suggest that post-exposure aciclovir may be less effective if administered too soon after exposure, although the issue has not been studied in a randomized fashion. Clinical disease occurred in a higher proportion of subjects who received aciclovir within 1–3 days compared with subjects in another study who used aciclovir after 7–9 days.^{50–52} Based on these data and because antiviral drugs are effective in treating VZV disease in immunocompromised patients, it appears reasonable to administer them during the incubation period if VZIG is not available. A regimen that has been proposed for immunocompromised patients is valaciclovir at 1000 mg three times daily given orally from Day 3 until Day 22 after exposure;⁴⁷ however, there are no published reports on the overall efficacy of this regimen. A theoretical concern is that the use of pre-emptive antiviral drugs may prolong the incubation period, similar to VZIG; however, there has been no report of such a phenomenon to date. Prolonged administration of post-exposure aciclovir or valaciclovir (Day 3–28 after exposure) has been suggested if these drugs are given in addition to VZIG.⁵³ The question of whether patients develop an immune response following post-exposure antiviral treatment has not been studied.

SEROPOSITIVE RECIPIENTS

Controversy exists as to whether a VZV-seropositive HCT recipient can be infected with a second strain and whether such infection can cause clinical disease. There are no published reports that prove conclusively that this can occur after HCT, but there is circumstantial evidence that secondary infections can occur, especially in patients with severe post-transplantation immunosuppression (e.g. following *in vivo* or *ex vivo* T-cell depletion or the use of high-dose corticosteroids⁴⁷). The use of post-exposure prophylaxis with valaciclovir appears reasonable in these circumstances.⁴⁷ Preventive strategies in different settings are summarized in Table 3.

Table 2: Proposed post-exposure prophylaxis drug regimens to prevent varicella zoster virus (VZV) disease

| Drug | Dose A, adult; P, paediatric | Start (days) of drug after exposure | Study design | n | Setting | Breakthrough VZV disease/ severity | Reference |
|--------------|---|---|---------------|----|------------------------|--|-----------|
| Aciclovir | 10–20 mg/kg, four times daily (P) | 7–9 | Observational | 25 | Children (IC) | 4 (16%)/mild | 50 |
| | 10 mg/kg, four times daily (P) | 1–3 | Observational | 13 | Children (IC) | 10 (77%)/severe 3 (21%)/mild | 52 |
| | | 7–9 | | 14 | | | |
| | 10 mg/kg, four times daily (P) ^a | 7 | Observational | 8 | Children (steroids) | 0 | 49 |
| Valaciclovir | 1000 mg, three times daily (A) | 3 | NR | NR | Adult/children (IC) | NR | 47 |

VZV, varicella zoster virus; IC, immunocompetent; NR, no published reports available for immunocompromised patients.
^aPatients also received varicella zoster virus-specific immunoglobulin.

Table 3: Summary of proposed preventive management of varicella zoster virus (VZV) in the haematopoietic cell transplantation (HCT) setting^{47,53}

| Setting | Preventive management |
|--|--|
| VZV-seronegative HCT candidates, caregivers and donors | • Vaccination 3–4 weeks before transplantation |
| Exogenous exposure | |
| VZV-seronegative HCT recipient | • VZIG within 96 h |
| | • Aciclovir or valaciclovir in combination with VZIG (Day 3–28) or alone (Day 3–22) if VZIG unavailable |
| VZV-seropositive HCT recipient | • Aciclovir or valaciclovir (Day 3–22) in patients with severe immunosuppression (high-dose steroids, <i>in vivo</i> or <i>ex vivo</i> T-cell depletion) |
| | • Post-exposure vaccination |
| Unvaccinated caregiver or family member during transplantation | • Avoid contact with transplant recipient during incubation time (Day 10–21) |
| | • If contact cannot be avoided: post-exposure aciclovir or valaciclovir (Day 8–22) |
| Reactivation disease | |
| VZV-seropositive HCT recipient | • Prophylaxis with aciclovir or valaciclovir for at least 1 year (for duration, also see ‘Current Strategies and Future Perspective’ in text) |

VZIG, varicella zoster immunoglobulin.

Current Strategies and Future Perspective

Chemoprophylaxis with aciclovir is highly effective in preventing VZV disease in VZV-seropositive HCT recipients. To date no case of resistance has been reported. Cases of VZV disease that occurred during or after prophylaxis generally responded to treatment doses of aciclovir or valaciclovir,^{43–46} suggesting that the emergence of drug resistance is not a significant problem to date. Perhaps the most important question today is how long to continue prophylaxis. A recent study by Thomson *et al.*⁴⁴ may be instructive in this context. In that study, HCT recipients received aciclovir (200 mg orally twice daily) until discontinuation of all immunosuppression and a CD4 T-cell count of 200 per mm³. VZV disease occurred in 40% of subjects at a median of 135 days (range 116–959) after discontinuation of aciclovir (Figure 2); 93% of the cases were dermatomal and no fatality occurred. Overall, the incidence of VZV disease equated to 34% at 5 years post-transplantation (Figure 2).⁴⁴ This study, although relatively small in size and uncontrolled, raises an interesting question: what should be the goal of chemoprophylaxis – eradication of all VZV disease or of *severe* disease? Towards the latter option, one could define the goal of chemoprophylaxis as prevention of fatal and disseminated disease rather than preventing all cases of disease. Support for this strategy comes from the observations that very late cases tend to be dermatomal and relatively mild in their clinical course and that fatalities due to VZV predominantly occur during the first year.² One could also hypothesize that clinical disease provides a stronger boost to T-cell immunity than subclinical reactivation on low-dose aciclovir. Issues of morbidity, possible hospitalization, post-infectious neuralgia and exposure of susceptible individuals remain, however. Thus, eradication of VZV seems desirable. The study by Thomson *et al.*⁴⁴ clearly suggests that the absence of immunosuppressive drugs and a CD4 count of greater than 200 per mm³ was inadequate to identify the optimal time to stop administering the drug. Thus, one option would be empirically to continue treatment for 6 additional

months (due to the observation that most cases occurred during this time-period). Another option would be to measure VZV-specific T-cell immunity using quantitative assays of T-cell immunity,⁵⁴ and to discontinue prophylaxis only when protective levels are reached. Studies are needed to evaluate this strategy. Since it will probably be difficult to generate a protective and lasting immune response in the presence of clinically active chronic graft-versus-host disease, a combined aciclovir and vaccination strategy is probably needed. This could be done with an inactivated vaccine that has been successfully used in autologous HCT recipients.⁵⁵ The live-attenuated varicella vaccine has been used 3 months after the discontinuation of immunosuppression in a small series of HCT recipients,⁵⁶ as well as in children with leukaemia in

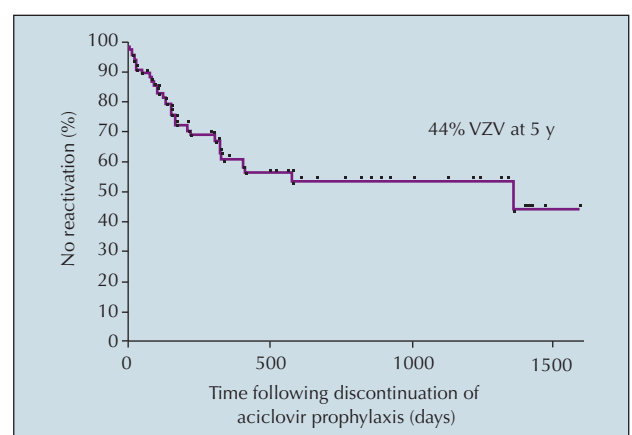


Figure 2: *Varicella zoster virus (VZV) disease among patients who received aciclovir prophylaxis (200 mg twice daily) for the duration of immunosuppression. The graph shows the cumulative incidence of VZV reactivation following discontinuation of aciclovir prophylaxis in 64 patients. Adapted from Thomson KJ et al. The effect of low-dose aciclovir on reactivation of varicella zoster virus after allogeneic haematopoietic stem cell transplantation. Bone Marrow Transplant 2005;35:1065–1069. Reproduced with permission from Nature Publishing Group.⁴⁴*

remission,¹² children after liver and intestinal transplantation,⁵⁷ and early- and intermediate stage HIV infection.^{58,59} This strategy should be approached with caution, however, due to reports of adverse outcomes.⁶⁰ Studies with the new zoster vaccine have not been reported in immunosuppressed patients to date.

Conclusions

Effective chemoprophylaxis and treatment are available for VZV, but there are a number of unresolved issues of VZV management in HCT recipients. With regard to chemoprophylaxis, issues include the following: is there a once-a-day regimen that prevents both VZV and HSV disease? What is the optimal strategy for long-term eradication of VZV disease? How can a combined antiviral drug and vaccination strategy be used to eradicate VZV disease?

With regard to the risk of clinical disease in vaccine-seropositive individuals, a population that will increasingly be referred to HCT, the following questions need to be addressed: what is the long-term risk of clinical disease? How long should prophylaxis be given in these patients? Is revaccination required?

It is conceivable that the live-attenuated vaccine virus possesses a lesser risk of clinical disease during long-term immunosuppression, thus permitting a shortened duration of chemoprophylaxis. The efficacy of the varicella vaccine is 87%,^{35,61} and a small but significant proportion of vaccine recipients may also harbour the wild-type virus, which may reactivate late after transplantation. Observational studies are needed to assess the risk in these patients. Prevention strategies are also needed for immunocompromised patient

populations other than HCT recipients, such as solid-organ transplant recipients^{10,11} and patients undergoing chemotherapy or other immunosuppressive therapies such as alemtuzumab.¹³ Evidence exists that chemoprophylaxis is also effective in these settings.⁶² In seronegative immunocompromised patients, post-exposure prophylaxis using antiviral drugs appears a reasonable approach to the management of exposure if VZIG is not available, but a randomized trial is needed to demonstrate non-inferiority before it can be recommended as a replacement.

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Conflicts of Interest

Michael Boeckh has served as a consultant for Novartis and Roche Laboratories.

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